HEMOLYSIS OF ERYTHROCYTES IN INTRAVENOUS INFUSION DEVICES: AN INTEGRATIVE REVIEW OF THE LITERATURE

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ABSTRACT: Extracorporeal hemolysis may be identified during hemotherapy. The nurse is one of the professionals responsible for the administration of blood components and the control of possible risks, and must therefore acquire the knowledge which supports clinical practice. The objective was to identify, in the literature, aspects related to hemolysis in concentrates of red blood cells resulting from the administration of blood through intravenous infusion devices. An Integrative Review of the Literature was undertaken, including articles in the English, Spanish and Portuguese languages, without limitation of data, indexed in four databases. A total of 12 (100.0%) scientific productions were selected, of which seven (58.3%) analyzed infusion pumps, two (16.7%) the handling of erythrocytes, two (16.7%) hemolysis with combinations of devices, and one (8.3%), the intravenous catheter. The results of four (33.3%) of these studies evidenced the occurrence of hemolysis. The studies indicated that hemolysis can occur during the passage of the component through infusion pumps and catheters.
DESCRIPTORS: Patient safety; Transfusion; Hemolysis; Erythrocytes; Intravenous infusions.

HEMÓLISE DE ERITRÓCITOS EM DISPOSITIVOS DE INFUSÃO INTRAVENOSA: REVISÃO INTEGRATIVA DA LITERATURA

RESUMO: Hemólise extracorpórea pode ser identificada durante processos hemoterápicos. O enfermeiro é um dos profissionais responsáveis pela administração de hemocomponentes e controle de possíveis riscos, portanto deve apropriar-se de conhecimentos que respaldem a prática clínica. O objetivo foi identificar na literatura aspectos relacionados à hemólise em concentrados de hemácias decorrentes de administração de sangue por dispositivos de infusão intravenosa. Realizou-se Revisão Integrativa da Literatura. Incluídos artigos na língua inglesa, espanhola e portuguesa, sem delimitação da data, indexados em quatro bases de dados. Foram selecionadas 12 (100,0%) produções científicas, sendo que em sete (58,3%) foram analisadas bombas de infusão, em duas (16,7%) a manipulação de eritrócitos, em duas (16,7%) a hemólise com combinações de dispositivos e em uma (8,3%) cateter intravenoso. Os resultados de quatro (33,3%) destes estudos evidenciaram ocorrência de hemólise. Os estudos apontaram que pode ocorrer hemólise durante a passagem do componente por bombas de infusão e cateteres.
DESCRITORES: Segurança do paciente; Transfusão; Hemólise; Eritrócitos; Infusões intravenosas.

HEMOLISIS DE ERITROCITOS EN DISPOSITIVOS DE INFUSIÓN: REVISIÓN INTEGRATIVA DE LA LITERATURA

RESUMEN: Hemolisis extracorpórea puede ser identificada durante procesos hemoterápicos. El enfermero es uno de los profesionales responsables por la administración de hemocomponentes y control de posibles riesgos, por lo tanto debe apropriarse de conocimientos para garantizar la práctica clínica. El objetivo fue identificar en la literatura aspectos de la hemolisis en concentrados de hematíes decurrentes de administración de sangre por dispositivos de infusión intravenosa. Fue realizada revisión integrativa de la literatura. Se utilizaron artículos en lengua inglesa, española y portuguesa, sin delimitación de fecha, indexados en cuatro bases de datos. Fueron seleccionadas 12 (100,0%) producciones científicas, siendo que en siete (58,3%) fueron analizadas bombas de infusión, en dos (16,7%) la manipulación de eritrocitos, en dos (16,7%) la hemolisis con combinaciones de dispositivos y en una (8,3%) catéter intravenoso. Los resultados de cuatro (33,3%) de estos estudios evidenciaron ocurrencia de hemolisis. Los estudios apuntaron que puede ocurrir hemolisis durante la pasaje del componente por bombas de infusión y catéteres.
DESCRIPTORES: Seguridad del paciente; Transfusión; Hemolisis; Eritrocitos; Infusiones intravenosas.

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INTRODUCTION

The history of hemotherapy is divided in two phases: empirical and scientific. In the empirical era, which extended until the 19th century, transfusions were undertaken from animals to human beings and between human beings, it being the case that nearly all these attempts ended in failure and the death of the recipients – and also of some donors. The scientific era, from the 20th century onwards, began with Karl Landsteiner's discoveries regarding the existence of blood groups and – later, in 1940 – when he described Rh Factor. These two discoveries were fundamental in the concept of compatibility between donors and recipients[1].

Modern hemotherapy has brought the idea of transfusing into the patient specific blood components, or only those which the patient needs, through the findings from clinical and laboratory data, thus opposing the use of whole blood. The concentrate of red blood cells, obtained following centrifugation and extraction of plasma from the unit of whole blood, is the blood component used most in clinical practice; its purpose is to increase the capacity for carriage of oxygen and the erythrocyte volume in patients with symptomatic anemia, being of significant use for cases of anemia and acute hemorrhage[2].

The red blood cell has the basic and vital function of transporting oxygen around the organism, through the hemoglobin. Besides the already-mentioned enzymes, the red blood cells have carbonic anhydrase, essential in the carriage of carbon dioxide until the lungs for its elimination, due to the chemical links between water and carbon dioxide. Hemoglobin also functions as a buffer system in the maintaining of the organism's acid-base balance[3].

During the hemotherapy processes, extracorporeal hemolysis can occur. This mainly takes place during the storage of the concentrate of red blood cells or due to mechanical trauma during the transfusion[4].

Injury of the red blood cells' membrane causes the liberation of hemoglobin in the plasma, in addition to which a high load of free potassium is liberated. Should free hemoglobin reach levels of 100 mg/dL in the plasma, elimination occurs through the urinary system, often causing hemoglobinuria. One possible final effect of this is kidney damage, which can progress to acute kidney failure. Furthermore, the liberation of potassium can lead to cardiac arrest and death, as this ion, free in the plasma in high concentrations, alters the electrical cardiac impulses and modifies their rhythm[3].

The administration of hemotherapy, in the majority of institutions, is the responsibility of the nurse, and this role is regulated by COFEN resolution N. 306/2006[5].

For the transfusion procedures, a series of intravenous infusion accessories is used, representing a group of materials which vary significantly in quality, price, presentation and recommendations for use.

Adverse events can be identified during the administration of blood components, compromising patient safety, the control of such events being an increasingly-addressed issue in the health area. Patient safety may be defined as health care which is free from harm, undertaken in the correct way, at the correct time, fairly and efficaciously, based in scientific knowledge and aiming to meet the comprehensive individual needs of the patient and family.

Blood transfusion is a critical process which must be undertaken with care measures which promote the prevention of infection, the correct identification of the patient, the correct choice of the accessories and devices for the transfusion therapy, control of the infusion and of the patient's clinical signs which may provide early indications of the occurrence of adverse events. However, in addition to such care measures, one must ensure that the product used is of quality and that it is beneficial for the patient's treatment. In this context, emphasis is placed on the importance of preventing the occurrence of extracorporeal hemolysis during the handling or infusion of blood components[6].

In order to provide support for the undertaking of experimental research on the issue, an integrative review was made of the literature, in order to identify studies produced regarding the administration of blood components. As a result, the objective was to identify, in the literature, aspects related to hemolysis resulting from blood transfusion using intravenous infusion devices.

METHOD

The type of study selected was an integrative review of the literature. Six stages of the

integrative literature review were used[7]: 1) Identification of the issue and selection of the hypothesis or research question; 2) Establishment of the criteria for inclusion and exclusion of studies/sampling or searching in the literature; 3) Definition of the information to be extracted from the studies selected/categorization of the studies; 4) Evaluation of the studies included in the integrative review; 5) Interpretation of the results; 6) Presentation of the review/summary of the knowledge.

The databases used were: Scientific Electronic Library Online (SCIELO), the US National Library of Medicine (PUBMED), Medical Literature Analysis and Retrieval System Online (MEDLINE) and The Cochrane Library (Cochrane).

In order to undertake the search for the scientific productions, the following descriptors were used in English in the four databases: hemolysis, blood cell, infusion devices, transfusion, intravenous infusion devices, and red blood cell. The following descriptors were also used in Portuguese in the SCIELO database: hemólise, eritrócitos, infusões intravenosas and transfusão de sangue. In the selection of the productions, the inclusion criteria were: productions in the English, Portuguese and Spanish languages, with no date of publication being defined. The identification of the relevance of the work in response to the research problem occurred through reading the studies' titles and abstracts.

Three inclusion criteria were used: firstly, the articles' language was considered (English, Portuguese and Spanish); subsequently, selection was undertaken based on the title and/or abstract, in response to the appropriacy of the topic of interest, and finally, the studies were evaluated through analysis of the content. The publications which were not in alignment with the inclusion criteria were excluded.

In total, 12 scientific productions were obtained, which were included in the review. The results are presented in the form of a table, containing a summary of the information extracted from the articles. Figure 1 shows how the selection of the articles in each database took place.

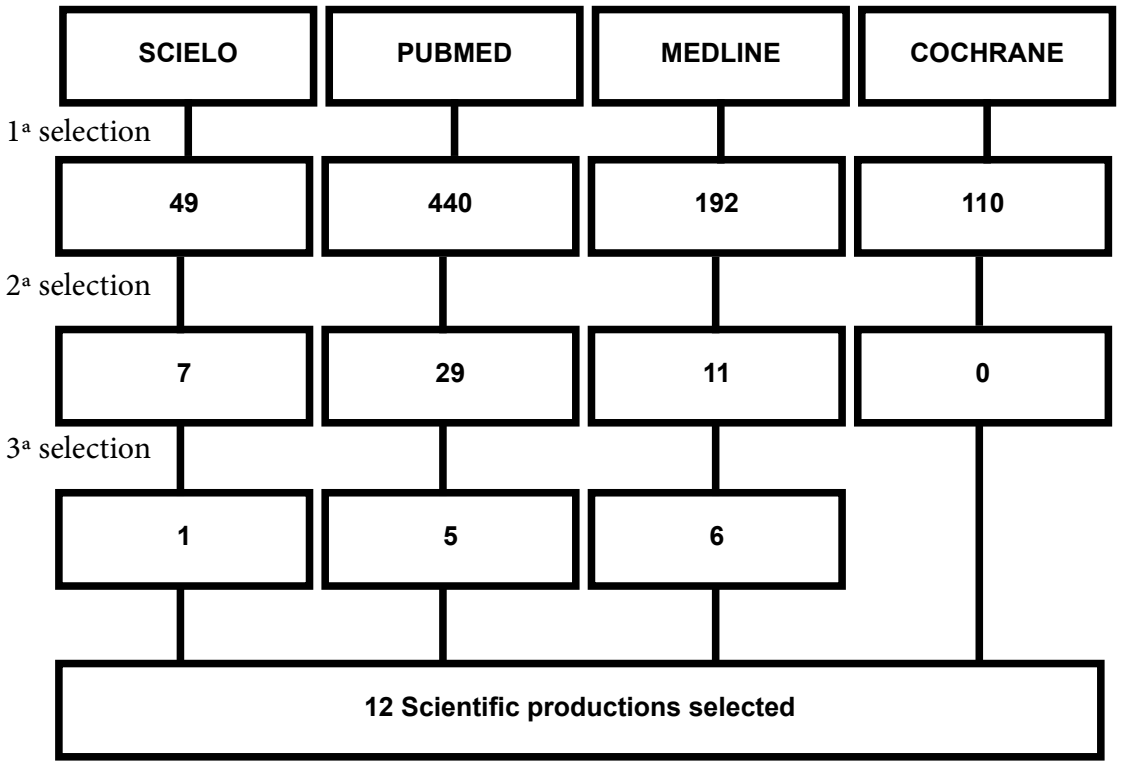

Figure 1 – Flowchart of the selection of the articles by database. 1st selection: research by descriptors; 2nd selection: reading of titles and abstracts, and 3rd selection: reading of the article in full.

RESULTS

Through the methodology used for the literature review, 12 articles were selected, of which 11 (91.6%) were from foreign literature, and one (8.4%) from the Brazilian literature; of these, six (50.0%) were produced in the United States of America (USA) one (8.4%) in Brazil, one (8.4%) in Holland, one (8.4%) in Denmark, one (8.4%) in Switzerland, one (8.4%) in Israel, and one (8.4%) in England. Among the studies selected for this review, the oldest dated from 1984, and the most recent was produced in 2012, as can be seen in Figure 2.

In Table 1, one can observe the summary of the articles selected for the study, presented in chronological order of publication.

Table 1 – Summary of the Selected Articles.

Authors/Locale	Method/Objective	Interventions	Results/ Conclusion
Gibson, JS Leff, RD Roberts, RJ [8] Iowa, USA – 1984	Experimental study on the effects of various intravenous systems (intravenous device and infusion pumps) on the integrity of the red blood cells;	Blood bags stored at 5ºC were left at room temperature for two hours for the experiment. Samples were collected prior to the infusion for control. A sample of 5ml was collected from each system immediately after the infusion, for analyses of the variables.	The speed of the infusion caused an increase of hemolysis proportional to the increase in speed, the peristaltic pump causing the greatest hemolysis at lower speeds.
Mateer, JR Perry, BW Tucker, JF Aprahamian, C[9] Wiscousin, USA - 1985	Experimental study on the effect of the wide bore intravenous catheter on hemolysis of the red blood cells, according to maximum flow rates and heating of the blood.	Obsolete blood bags (37 days) with hematocrit of 45% were subjected to compression through a pressurizer, with pressures of 300 and 600 mmHg being generated, with flow of 100 ml/h. Samples were collected subsequent to the infusion for analyses of the variables.	The blood component in place in the intravenous device was administered according to the pressures used, however, the warming of the blood significantly reduced the infusion flow. There was no significant hemolysis.
Thompson, HW Lasky, LC Polesky, HF (10) Minnesota, USA - 1986	Experimental study regarding the adjustability of the volumetric infusion pump for infusion of concentrate of red blood cells.	Blood bags stored for 35 days were infused at a speed of 300 to 850 ml/h. Tests were undertaken prior to the infusion for control, and subsequent to the infusion for analysis of the variables of interest.	The free hemoglobin in the plasma increased after the infusion of blood cells, although there was no significant hemolysis.

Burch, KJ Phelps, SJ Constance, TD(11) Tennessee, USA - 1991	Experimental study on the effect of the linear peristaltic infusion pump on the integrity of the concentrates of red blood cells and whole blood during the transfusion.	The infusion speeds used varied from 5 to 999 ml/h with fresh red blood cells (72 hours after donation) and old red blood cells (72 hours after the expiry date). The blood was stored at a temperature of 5°C up until the day of the study, and on the day of the experiment, it was left for two hours at room temperature prior to use. Pre- and post-infusion samples were collected for analysis of the variables.	There was no significant percentage of hemolysis in any of the trials undertaken, either with fresh red blood cells or with old red blood cells.
Hansen, TG Sprogoe-Jacobse , U Pedersen, C. M Skovgaard Olsen, K Risom Kristensen, S (12) Dennmark – 1998	Experimental study on the effect of different infusion pumps on the quality of the red blood cells after transfusion.	The study used blood cells stored for 8 to 11 days, and blood cells stored for 25 to 33 days. Pumps with peristaltic mecanism (6.9 ml/s) and syringe pumps (300 mmHg – 2.9 ml/s) were used. The blood bags were stored at 4°C and infused over 30 minutes randomly by any one of the pumps.	Older blood cells had a higher value of free Hb, free potassium and LDH and presented higher hematocrit. There were no significant differences in the hemolysis according to infusion pumps and time of storage of the blood cells. Newer blood cells presented a small increase in the percentage of hemolysis and in the LDH.
Frelich, R Ellis, MH (13) Tel Aviv, Israel - 2001	Experimental study on the effect of the external pressurizer and of the diameter of the catheter on the extent of hemolysis of units of red blood cells.	The study used bags of concentrates from fresh (~10.8 days) and old (~28.9 days) red blood cells. Each unit was transfused through catheters with bores of 16G, 18G, 20G and 22G and the final 5 ml of the transfusion were collected. The transfusions in each catheter were undertaken without the pneumatic pressurizer, and were compared with the use of the external pneumatic pressurizer, with pressures of 150 mmHg and 300 mmHg.	The degree of hemolysis induced by application of external pressure was similar between old and fresh units. The external pressurizer was considered safe in practice as it did not cause significant hemolysis.

Frey, B Eber, S Weiss, M (14) Zurich, Switzerland - 2003	Experimental study on the effects of three different infusion pumps on the integrity of the red blood cells.	The storage of the blood bags varied from 18 to 46.5 days. The units were leukoreduced by filtration, stored at 4°C, and left at room temperature for one hour prior to the experiment. The study tested syringe pumps, conventional peristaltic pumps, and a volumetric pump with a shuttle mechanism. The flow used was 20ml/h and the duration of the infusion was 2.5 hours. The experiments were repeated with each pump with eight different units of blood cells. In the final part of the infusion device of the three pumps, a 24G catheter was connected and venous pressure at 15 mmHg at 20 cm above the pumps was simulated.	The greater the time of storage, the greater the concentrations of plasma potassium and hemoglobin, osmotic fragility and mean corpuscular volume (MCV). In the analysis of all the experimental trials with the three infusion pumps, the plasma hemoglobin, potassium, LDH and bilirubin increased significantly after the infusion, the syringe and peristaltic pumps presented an increase in the concentrations of plasma hemoglobin and LDH compared with the volumetric pump. Significant hemolysis was observed in the study, the volumetric pump being the least hemolytic.
Carvalho, EB Borges, EL Carlos, LMB Silva, MAM Magalhães, SMM Gomes, FVBAF Carvalho, MJC Quixadá, ATS Pitobeira, MHS [4] Ceará, Brazil – 2007	Experimental study on the extent of hemolysis of concentrate of red blood cells stored for less than 10 days, caused by infusion pumps.	One pump with a rotatory peristaltic mechanism, and two with linear peristaltic mechanisms, of different brands, were used. The infusion speeds of 120 ml/h, 240 ml/h and 360 ml/h were tested. Samples were collected prior to the passage through the infusion pump, half way through the procedure, and at the end of the procedure, for analysis of the variables.	In the present study, it was observed that the different models mechanisms of pumps for infusion of solutions (Linear peristaltic and rotatory peristaltic), time and speeds, (V1, V2, V3) did not cause significant changes in the parameters analyzed, which evidence hemolysis in the concentrates of red blood cells, that is, levels of free hemoglobin and plasma potassium.

Parfitt, HS Davies, SV Tighe, P Ewings, P (15) England - 2007	Experimental study on the harm in red blood cells caused by two infusion pumps with peristaltic mechanisms.	The experiments were held with fresh blood (9 days), intermediate (28 days) and on the expiry date (35 days). The blood was stored at 4°C and was used 20 minutes after being taken out of the refrigerator. The infusion speeds were: 40 ml/h infused over 4 hours and 150 ml/h infused over 2 hours. Tests were undertaken with a gravitational device. The samples from the two pumps and the gravitational device were collected in tubes of heparin and EDTA.	The free potassium increased from 18.7 mmolL-1 on the 9th day to 44.1 mmolL-1 on the 28th day and to 48.5 mmolL-1 on the 35th day. The free Hb had a significant increase in the blood bags with a longer period of storage; the infusion speeds did not significantly influence the hemolysis. The pumps had greater hemolytic potential, mainly in blood stored for longer, but there were no significant results for hemolysis. The analyses of the gravitational samples demonstrated zero rate for potassium and free hemoglobin.
Lieshout-Krikke, RW Van der Meer, PF Koopman, MMW Korte, D (16) Amsterdam, Netherlands - 2011	Experimental study on the in vitro quality of red blood cells after passing through the peristaltic volumetric infusion pump.	A control test was undertaken with gravitational infusion. The infusion speeds were 100 and 300 ml/h. The concentrates of red blood cells had been stored for 30 and 35 days. At the end of the infusion line, a transfer bag was connected and the samples of the two rates of flow were collected in vitro for measuring.	None of the infusion pumps induced increase in free Hb, annexin A5 binding or formation of erythrocytes in comparison with the blood cells from the control samples.

Hod, EA Brittenham, GM Billote, GB Francis, RO Ginzburg,YZ Hendrickson, JE et al (17) New York, USA – 2011	Experimental study on the storage effect with units of red blood cells regarding the rate of hemolysis and changes in blood parameters.	Collection was made through apheresis and autologous transfusion. Each donor was transfused after 3 to 7 days of storage and after 40 to 42 days of storage. The infusion speedy was 150 ml/h. The samples were collected 90 minutes prior to the transfusion, immediately at the start of the transfusion and 1, 2, 4, 24 and 72 hours post-transfusion.	Extravascular hemolysis: compared with the transfusion of fresh units, transfusions of old units were associated with a significant increase of total bilirubin in the serum, with increase peaking after four hours of the transfusion. There was an increase of free hemoglobin as time passed. There was no significant difference between fresh and old units in the levels of haptoglobin in the serum and LDH. There was an increase of iron in the serum and in the transferrin in the old units.
Ley, JT Yazer, MH Waters, JH (18) Pennsylvania, USA - 2012	Experimental study, aiming to evaluate and compare the characteristics of the red blood cells which are lost and reinfused in total knee replacement surgery, in which they were reprocessed by two different devices: which wash prior to reinfusion and which do not undertake the washing.	The patients were divided into groups; group 1 (washed group) were operated on by surgeons who use the device which washes erythrocytes, and group 2 (unwashed group) were operated on by surgeons who did not use equipment with washing of erythrocytes. Samples were collected during the re-infusion of the recovered blood. The sanples were centrifuged and the supernatant was evaluated.	Group 1 presented a rate of free hemoglobin in the plasma greater than that of group 2. The difference in the rate of hemolysis between the groups was not statistically significant. The membrane fragility index (MFI) was greater in group 1. It was concluded that the group which used the washing of erythrocytes prior to the reinfusion presented a higher rate of Hb and MFI, and therefore a higher rate of hemolysis.

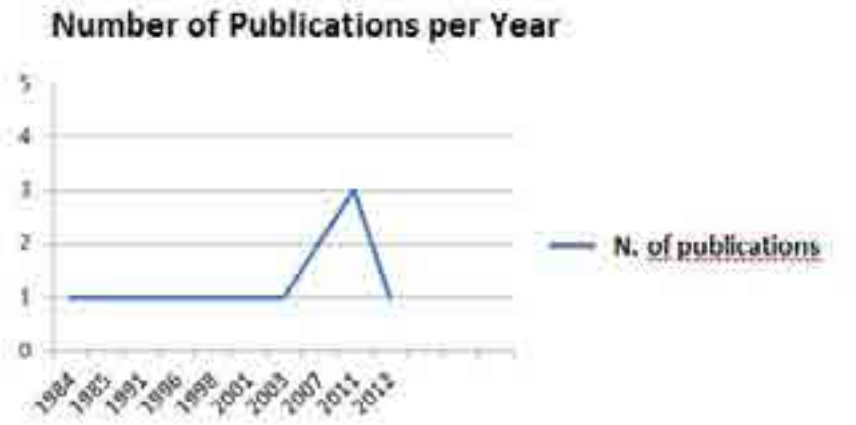

Figure 2 – Number of studies available in the literature on the handling and infusion of erythrocytes and hemolysis, by year of publication.

Of the 12 articles analyzed, in seven (58.3%) infusion pumps were used, two (16.6%) address procedures on handling of erythrocytes, one (8.3%) tested intravenous devices, and two (16.6%) studied hemolysis with combinations of devices. In order to facilitate understanding, the studies were separated in categories. The categories and the studies included in each one are shown below.

Infusion pumps

The experiments which evaluated the relation between hemolysis and the administration of blood components in infusion pumps were undertaken with volumetric and syringe infusion pumps, with peristaltic, linear or rotatory mechanisms, and infusion speeds which varied from 5 ml/h to 999 ml/h. In these studies, the concentrates of red blood cells analyzed were stored for periods from 0 to 42 days.

Of the seven studies which evaluated infusion pumps, only one (14.28%) evidenced hemolysis in the pumps used; however, all studies recommend further studies and evaluations of new pumps for recommendation of good practices.

Intravenous Devices

One study analyzed the application of pressures of 300 and 600 mmHg in red blood cells stored for 37 days at an infusion speed of 100 ml/h. In evaluating hemolysis in a wide-bore intravenous catheter, with high infusion speeds and pressures, there was no significant hemolysis in any of the sample studied. This study evidenced that the only problem in applying high rates of flow and pressure in the blood is that there is warming of the cells, which results in reduction of the infusion flow. Of the studies with intravenous devices, none evidenced high rates of hemolysis.

Combination of Devices

Among the 12 articles selected, two involved experiments with combinations of devices. The first study presented that the peristaltic pump caused more hemolysis than the others and that the infusion speed of 50 ml/h presented a greater degree of hemolysis. Although hemolysis was identified in another study, there was no significant value, or greater than 1%.

Handling of Erythrocytes

In the two studies on the handling of erythrocytes, there was identification of hemolysis during the handling. Among the techniques which caused hemolysis, emphasis is placed on the washing of red blood cells and the prolonged storage of blood cells.

General Evaluation of the Studies

Of the 12 scientific productions selected, 33.3% (four) had positive results for hemolysis.

The equipment which caused hemolysis was the infusion pumps, and the techniques used with blood which caused hemolysis were: transfusion of blood following washing of blood cells and separation of blood components.

DISCUSSION

Regarding the occurrence of hemolysis, the first problem of clinical significance is related to the increase of free hemoglobin which the reticuloendothelial system does not manage to remove, causing hemoglobinemia with possible consequences for the renal system. Another potential problem of hemolysis is the excess of potassium liberated to the extracellular environment, which, in its turn, can cause arrhythmias and, in serious cases, even cardiac arrest and death[19].

The studies selected for this review show that hemolysis occurs in the processes of handling the erythrocytes prior to transfusion (washing and storage), and also in the passage through the infusion pumps and catheters. It was evidenced that hemolysis is not dependent on the infusion speed, and always occurred in accordance with the increase in storage time.

The units of blood components may be administered using specific blood transfusion devices (with attached filters in the drip chamber) and through infusion pumps of various types and mechanisms, which have infusion systems with different configurations. The technical regulation of hemotherapy procedures is defined in Ministerial Ordinance N. 2712/2013, which presents guidance regarding infusion devices and techniques[20].

In the analysis of the studies, one can state that the volumetric infusion pump was the least hemolytic, if compared with the syringe pump and those with peristaltic pump. One potential problem, for the classification of infusion pumps in the studies, was that each one evidences the infusion pump in a particular way, some studies state which type of infusion pump they are analyzing, and others, only which mechanism. In the studies of infusion pumps, those with peristaltic mechanisms were more hemolytic, however, adequate distinction was not evidenced between the volumetric pumps and those with peristaltics pumps.

Integrative reviews of the literature aim to identify evidence on specified themes which are intended to be studied. In analyzing the studies, it is possible to conclude that: published studies were not found which deal with the effects of the micro drip and macro drip sets on the red blood cells during a blood transfusion; this fact strengthens the importance of undertaking research for these devices. In some studies, the device, or the gravitational infusion, is used as control for tests of other equipment; however, there is no detailing of the results of the analyses made with these devices, and there is no description in the literature regarding their actual effect on the red blood cells[21].

The second observation was the low number of publications on the issue, besides the fact that in the majority of cases the results are inconclusive or disagree with each other, and that at the time of writing there are no defined standards for equipment with guaranteed safety; for this reason, a greater number of studies is necessary, with greater quality in their methodologies.

The third observation was in relation to the types of studies present. One can note that the majority of studies are related to infusion pumps and handling of erythrocytes, but that there are no studies on infusion pumps with peristaltics meacanism, implying further necessity for experimental research regarding such equipment.

CONCLUSIONS

The studies selected for this review show that hemolysis occurs in the processes of handling of erythrocytes and also in the passage through the infusion pumps and catheters. It was evidenced that the hemolysis is not dependent on the infusion speed, and always occurs in accordance with the increase in storage time. These studies evidence that, among the different types of infusion pump, the volumetric infusion pump caused the lowest level of hemolysis.

In accordance with the conclusions of nearly all the studies addressed, it was seen that within this line of research, there is still much to be studied and evaluated in terms of safety in the transfusion of concentrate of red blood cells by gravitational or automated equipment. It is

certain that the results presented are capable of supporting further research, such that these may be scientifically-based and relevant in the context of clinical practice, raising the concept of patient safety and improvement in the nurses' care practice.

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